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(54) Title: INHIBITION OF COCLOOXYGENASE-3 MEDIATED DISEASES AND DISORDERS

(57) Abstract: The invention describes methods for treating and/or preventing diseases and/or disorders resulting from elevated levels of cyclooxygenase-3 comprising administration of at least one cyclooxygenase inhibitor that is optionally nitrosated and/or nitrosylated, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase and/or at least one therapeutic agent. The invention also provides methods for treating and/or preventing diseases and/or disorders resulting from elevated levels of cyclooxygenase-3 comprising administration of at least compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and, optionally, at least one therapeutic agent. The invention also provides methods for treating and/or improving the gastrointestinal properties of cyclooxygenase-2 (COX-2) selective inhibitors; for treating and/or preventing renal and other toxicities of COX-2 selective inhibitors; for treating and for improving the cardiovascular profile of COX-2 selective inhibitors comprising administration of at least one cyclooxygenase-3 (COX-3) inhibitor that is optionally nitrosated and/or nitrosylated, and, optionally, at least nitric oxide donor and/or at least one therapeutic agent. The cyclooxygenase inhibitors of the invention include, but are not limited to, cyclooxygenase-3 selective inhibitors, cyclooxygenase-2 selective inhibitors, cyclooxygenase-1 selective inhibitors, non-steroidal anti-inflammatory compounds, and mixtures of two or more thereof.

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INHIBITION OF CYCLOOXYGENASE-3 MEDIATED DISEASES AND DISORDERS

FIELD OF THE INVENTION

The invention describes methods for treating and/or preventing diseases and/or disorders resulting from elevated levels of cyclooxygenase-3 comprising administration of at least one cyclooxygenase inhibitor that is optionally nitrosated and/or nitrosylated, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase and/or at least one therapeutic agent. The invention also provides methods for treating and/or preventing diseases and/or disorders resulting from elevated levels of cyclooxygenase-3 comprising administration of at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and, optionally, at least one therapeutic agent. The invention also provides methods for treating and/or improving the gastrointestinal properties of cyclooxygenase-2 (COX-2) selective inhibitors; for treating and/or preventing renal and/or respiratory toxicities of COX-2 selective inhibitors; for treating and for improving the cardiovascular profile of COX-2 selective inhibitors comprising administration of at least one cyclooxygenase-3 (COX-3) inhibitor that is optionally nitrosated and/or nitrosylated, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase and/or at least one therapeutic agent. The cyclooxygenase inhibitors of the invention include, but are not limited to, cyclooxygenase-3 selective inhibitors, cyclooxygenase-2 selective inhibitors, cyclooxygenase-1 selective inhibitors, non-steroidal anti-inflammatory compounds, and mixtures of two or more thereof.

BACKGROUND OF THE INVENTION

Nonsteroidal anti-inflammatory compounds (NSAIDs) are widely used for the treatment of pain, inflammation, and acute and chronic inflammatory disorders such as osteoarthritis and rheumatoid arthritis. These compounds inhibit the activity of the enzyme cyclooxygenase (COX), also known as prostaglandin G/H synthase, which is the enzyme that converts arachidonic acid into prostanoids. The NSAIDs also inhibit

the production of other prostaglandins, especially prostaglandin G_2, prostaglandin H_2 and prostaglandin E_2, thereby reducing the prostaglandin-induced pain and swelling associated with the inflammation process. The chronic use of NSAIDs has been associated with adverse effects, such as gastrointestinal ulceration and renal toxicity. The undesirable side effects are also due to the inhibition of prostaglandin in the affected organ.

Two isoforms of cyclooxygenase, encoded by two distinct genes (Kujubu et al, *J. Biol. Chem.*, 266, 12866-12872 (1991)), have been identified – a constitutive form, cyclooxygenase-1 (COX-1), and an inductive form, cyclooxygenase-2 (COX-2). It is thought that the antiinflammatory effects of NSAIDs are mediated by the inhibition of COX-2, whereas the side effects seem to be caused by the inhibition of COX-1. The NSAIDs currently on the market either inhibit both isoforms of COX with little selectivity for either isoform or are COX-1 selective. Compounds that are COX-2 selective inhibitors have been developed and marketed. These COX-2 selective inhibitors have the desired therapeutic profile of an antiinflammatory drug without the adverse effects commonly associated with the inhibition of COX-1. However, these compounds can result in dyspepsia and can cause gastropathy (Mohammed et al, *N. Engl. J. Med.*, 340(25) 2005 (1999)). Additionally the COX-2 selective inhibitors can increase the risk of cardiovascular events in a patient (Mukherjee et al., *JAMA* 286(8) 954-959 (2001)); Hennan et al., *Circulation*, 104:820-825 (2001)).

Recently a third isoform of cyclooxygenase, COX-3, has been proposed (Willoughby et al., *Lancet*, 355(9204) 646-648 (2000); Botting, *Clinical Infectious Diseases*, 31:S202-210 (2000); Chandrasekharan et al., *Proc. Natl. Acad. Sci.*, 99:13926-13931 (2002). It is postulated that the cyclooxygenase-3 enzyme may be a product of the same gene that encodes the cyclooxygenase-2 enzyme but has different molecular characteristics.

There is still a need in the art for the treatment and/or prevention of diseases and disorders resulting from elevated levels of cyclooxygenase-3. The invention is directed to these, as well as other, important ends.

SUMMARY OF THE INVENTION

The invention provides methods for treating and/or preventing cyclooxygnease-3 (COX-3) mediated disorders (i.e., disorders resulting from elevated levels of COX-3) in a patient in need thereof which comprises administering to a patient a therapeutically effective amount of at least one cyclooxygenase inhibitor,

that is optionally substituted with at least one NO and/or NO_2 group (i.e., nitrosylated and/or nitrosated), and, optionally, at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO^+) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase (i.e. NO donor). The methods can optionally further comprise the administration of at least one therapeutic agent, such as, for example, steroids, nonsteroidal antiinflammatory compounds (NSAID), 5-lipoxygenase (5-LO) inhibitors, leukotriene B_4 (LTB_4) receptor antagonists, leukotriene A_4 (LTA_4) hydrolase inhibitors, 5-HT agonists, HMG CoA inhibitors, H_2 antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and mixtures of two or more thereof. The COX inhibitors, can be nitrosated and/or nitrosylated through one or more sites, such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen. In this embodiment of the invention, the methods can involve administering the COX inhibitors, that are optionally nitrosated and/or nitrosylated, administering the COX inhibitors, that are optionally nitrosated and/or nitrosylated, and NO donors, administering the COX inhibitors, that are optionally nitrosated and/or nitrosylated, and therapeutic agents, or administering the COX inhibitors, that are optionally nitrosated and/or nitrosylated, NO donors, and therapeutic agents. The COX inhibitors, nitric oxide donors, and/or therapeutic agents can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

Another embodiment of the invention provides methods for treating and/or preventing cyclooxygnease-3 (COX-3) mediated disorders (i.e., disorders resulting from elevated levels of COX-3) in a patient in need thereof which comprises administering to the patient a therapeutically effective amount of at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO^+) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase (i.e. NO donor). The methods can optionally further comprise the administration of at least one therapeutic agent, such as, for example, steroids, nonsteroidal antiinflammatory compounds (NSAID), 5-

lipoxygenase (5-LO) inhibitors, leukotriene B_4 (LTB_4) receptor antagonists, leukotriene A_4 (LTA_4) hydrolase inhibitors, 5-HT agonists, HMG CoA inhibitors, H_2 antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and mixtures of two or more thereof. In this embodiment of the invention, the methods can involve administering the NO donors, administering the NO donors, and therapeutic agents. The nitric oxide donors, and/or therapeutic agents can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carrier.

Another embodiment of the invention provides methods for treating and/or improving the gastrointestinal properties of cyclooxygenase-2 (COX-2) selective inhibitors; and for treating and/or preventing renal and/or respiratory toxicity of cyclooxygenase-2 (COX-2) selective inhibitors in a patient in need thereof which comprises administering to the patient a therapeutically effective amount of at least one COX-3 selective inhibitor, that is optionally substituted with at least one NO and/or NO_2 group (i.e., nitrosylated and/or nitrosated), and, optionally, at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO^+) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase (i.e. NO donor). The methods can optionally further comprise the administration of at least one therapeutic agent, such as, for example, steroids, nonsteroidal antiinflammatory compounds (NSAID), 5-lipoxygenase (5-LO) inhibitors, leukotriene B_4 (LTB_4) receptor antagonists, leukotriene A_4 (LTA_4) hydrolase inhibitors, 5-HT agonists, HMG CoA inhibitors, H_2 antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and mixtures of two or more thereof. The COX-3 inhibitor can be nitrosated and/or nitrosylated through one or more sites, such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen. In this embodiment of the invention, the methods can involve administering the COX-3 inhibitors, that are optionally

nitrosated and/or nitrosylated, administering the COX-3 inhibitors, that are optionally nitrosated and/or nitrosylated, and NO donors, administering the COX-3 inhibitors, that are optionally nitrosated and/or nitrosylated, and therapeutic agents, or administering the COX-3 inhibitors, that are optionally nitrosated and/or nitrosylated, NO donors, and therapeutic agents. The COX-3 inhibitors, nitric oxide donors, and/or therapeutic agents can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

Yet another embodiment of the invention provides methods for improving the cardiovascular profile of COX-2 selective inhibitors in a patient in need thereof which comprises administering to the patient a therapeutically effective amount of at least one COX-3 selective inhibitor, optionally substituted with at least one NO and/or NO_2 group (i.e., nitrosylated and/or nitrosated), and, optionally, at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO^+) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase (i.e. NO donor). The methods can optionally further comprise the administration of at least one of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, and mixtures of two or more thereof. In this embodiment of the invention, the methods can involve administering the nitrosated and/or nitrosylated COX-3 selective inhibitors, administering the COX-3 selective inhibitors, that are optionally nitrosated and/or nitrosylated, and NO donors, administering the COX-3 selective inhibitors, that are optionally nitrosated and/or nitrosylated, and at least one of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, antiplatelet agents, thrombin inhibitors or thromboxane inhibitors, or administering the COX-3 selective inhibitors, that are optionally nitrosated and/or nitrosylated, NO donors, and at least one of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, antiplatelet agents, thrombin inhibitors or thromboxane inhibitors. The COX-3 inhibitors, nitric oxide donors, and/or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, antiplatelet agents, thrombin inhibitors or thromboxane inhibitors can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

DETAILED DESCRIPTION OF THE INVENTION

As used throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

"Cyclooxygenase (COX) inhibitor" refers to a compound that inhibits any cyclooxygenase enzyme, including, but not limited to cyclooxygenase-1 enzyme, cyclooxygenase-2 enzyme and/or cyclooxygenase-3 enzyme and mixtures of two or more thereof. "COX inhibitors" include, for example, NSAIDs, cyclooxygenase-1 (COX-1) selective inhibitors, cyclooxygenase-2 (COX-2) selective inhibitors, cyclooxygenase-3 (COX-3) selective inhibitors, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) selective inhibitors, cyclooxygenase-1 (COX-1) and cyclooxygenase-3 (COX-3) selective inhibitors, cyclooxygenase-2 (COX-2) and cyclooxygenase-3 (COX-3) selective inhibitors, cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2) and cyclooxygenase-3 (COX-3) selective inhibitor and the like.

"NSAID" refers to a nonsteroidal anti-inflammatory compound or a nonsteroidal anti-inflammatory drug. NSAIDs inhibit cyclooxygenase, the enzyme responsible for the biosyntheses of the prostaglandins and certain autocoid inhibitors, including inhibitors of the various isozymes of cyclooxygenase (including but not limited to cyclooxygenase-1 and -2), and as inhibitors of both cyclooxygenase and lipoxygenase

"Cyclooxygenase-2 (COX-2) selective inhibitor" refers to a compound that selectively inhibits the cyclooxygenase-2 enzyme over the cyclooxygenase-1 enzyme. In one embodiment, the compound has a cyclooxygenase-2 IC_{50} of less than about 2 μM and a cyclooxygenase-1 IC_{50} of greater than about 5 μM, in the human whole blood COX-2 assay (as described in Brideau et al., *Inflamm Res.*, 45: 68-74 (1996)) and also has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 10, and preferably of at least 40. In another embodiment, the compound has a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and preferably of greater than 20 μM. The compound can also inhibit the enzyme, lipoxygenase. Such selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

"Cyclooxygenase-3 (COX-3) selective inhibitor" refers to a compound that selectively inhibits the cyclooxygenase-3 enzyme over the cyclooxygenase-1 enzyme or the cyclooxygenase-2 enzyme.

"Therapeutic agent" includes any therapeutic agent that can be used to treat or prevent the diseases described herein. "Therapeutic agents" include, for example, steroids, nonsteroidal antiinflammatory compounds, 5-lipoxygenase inhibitors, leukotriene B_4 receptor antagonists, leukotriene A_4 hydrolase inhibitors, 3-hydroxy-3-methylglutaryl coenzyme A inhibitors, H_2 antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and the like. Therapeutic agent includes the pro-drugs and pharmaceutical derivatives thereof including but not limited to the corresponding nitrosated and/or nitrosylated derivatives. Although nitric oxide donors have therapeutic activity, the term "therapeutic agent" does not include the nitric oxide donors described herein, since nitric oxide donors are separately defined.

"Cardiovascular disease or disorder" refers to any cardiovascular disease or disorder known in the art, including, but not limited to, restenosis, atherosclerosis, atherogenesis, angina, (particularly chronic, stable angina pectoris), ischemic disease, congestive heart failure or pulmonary edema associated with acute myocardial infarction, thrombosis, controlling blood pressure in hypertension (especially hypertension associated with cardiovascular surgical procedures), thromboembolic events, platelet aggregation, platelet adhesion, smooth muscle cell proliferation, vascular complications associated with the use of medical devices, wounds associated with the use of medical devices, cerebrovascular ischemic events, and the like. Complications associated with the use of medical devices may occur as a result of increased platelet deposition, activation, thrombus formation or consumption of platelets and coagulation proteins. Such complications, which are within the definition of "cardiovascular disease or disorder," include, for example, myocardial infarction, ischemic stroke, transient ischemic stroke, thromboembolic events, pulmonary thromboembolism, cerebral thromboembolism, thrombophlebitis, thrombocytopenia, bleeding disorders and/or any other complications which occur either directly or indirectly as a result of the foregoing disorders.

"Restenosis" is a cardiovascular disease or disorder that refers to the closure of a peripheral or coronary artery following trauma to the artery caused by an injury such as, for example, angioplasty, balloon dilation, atherectomy, laser ablation treatment or stent insertion. Restenosis can also occur following a number of invasive surgical

techniques, such as, for example, transplant surgery, vein grafting, coronary artery bypass surgery, endarterectomy, heart transplantation, balloon angioplasty, atherectomy, laser ablation, endovascular stenting, and the like.

"Atherosclerosis" is a form of chronic vascular injury in which some of the normal vascular smooth muscle cells in the artery wall, which ordinarily control vascular tone regulating blood flow, change their nature and develop "cancer-like" behavior. These vascular smooth muscle cells become abnormally proliferative, secreting substances such as growth factors, tissue-degradation enzymes and other proteins, which enable them to invade and spread into the inner vessel lining, blocking blood flow and making that vessel abnormally susceptible to being completely blocked by local blood clotting, resulting in the death of the tissue served by that artery. Atherosclerotic cardiovascular disease, coronary heart disease (also known as coronary artery disease or ischemic heart disease), cerebrovascular disease and peripheral vessel disease are all common manifestations of atherosclerosis and are therefore encompassed by the terms "atherosclerosis" and "atherosclerotic disease".

"Improving the cardiovascular profile" refers to and includes reducing the risk of thromboembolic events, reducing the risk of developing atherosclerosis and atherosclerotic diseases, and inhibiting platelet aggregation of the parent COX-2 inhibitor.

"Thromboembolic events" includes, but is not limited to, ischemic stroke, transient ischemic stroke, myocardial infarction, angina pectoris, thrombosis, thromboembolism, thrombotic occlusion and reocclusion, acute vascular events, restenosis, transient ischemic attacks, and first and subsequent thrombotic stroke. Patients who are at risk of developing thromboembolic events, may include those with a familial history of, or genetically predisposed to, thromboembolic disorders, who have had ischemic stroke, transient ischemic stroke, myocardial infarction, and those with unstable angina pectoris or chronic stable angina pectoris and patients with altered prostacyclin/thromboxane A_2 homeostasis or higher than normal thromboxane A_2 levels leading to increase risk for thromboembolism, including patients with diabetes and rheumatoid arthritis.

"Thromboxane inhibitor" refers to any compound that reversibly or irreversibly inhibits thromboxane synthesis, and includes compounds which are the so-called thromboxane A_2 receptor antagonists, thromboxane A_2 antagonists, thromboxane A_2/prostaglandin endoperoxide antagonists, thromboxane receptor (TP)

antagonists, thromboxane antagonists, thromboxane synthase inhibitors, and dual acting thromboxane synthase inhibitors and thromboxane receptor antagonists. The characteristics of the preferred thromboxane inhibitor should include the suppression of thromboxane A_2 formation (thromboxane synthase inhibitors) and/or blockade of thromboxane A_2 and prostaglandin H_2 platelet and vessel wall (thromboxane receptor antagonists). The effects should block platelet activation and therefore platelet function.

"Thromboxane A_2 receptor antagonist" refers to any compound that reversibly or irreversibly blocks the activation of any thromboxane A_2 receptor.

"Thromboxane synthase inhibitor" refers to any compound that reversibly or irreversibly inhibits the enzyme thromboxane synthesis thereby reducing the formation of thromboxane A_2. Thromboxane synthase inhibitors may also increase the synthesis of antiaggregatory prostaglandins including prostacyclin and prostaglandin D_2. Thromboxane A_2 receptor antagonists and thromboxane synthase inhibitors and can be identified using the assays described in Tai, Methods of Enzymology, Vol. 86, 110-113 (1982); Hall, *Medicinal Research Reviews,* 11:503-579 (1991) and Coleman et al., *Pharmacol Rev.*, 46: 205-229 (1994) and references therein, the disclosures of which are incorporated herein by reference in its entirety.

"Dual acting thromboxane receptor antagonist and thromboxane synthase inhibitor" refers to any compound that simultaneously acts as a thromboxane A_2 receptor antagonist and a thromboxane synthase inhibitor.

"Thrombin inhibitors" refers to and includes compounds that inhibit hydrolytic activity of thrombin, including the catalytic conversion of fibrinogen to fibrin, activation of Factor V to Va, Factor VIII to VIIIa, Factor XIII to XIIIa and platelet activation. Thrombin inhibitors may be identified using assays described in Lewis et at., Thrombosis Research. 70: 173-190 (1993).

"Platelet aggregation" refers to the binding of one or more platelets to each other. Platelet aggregation is commonly referred to in the context of generalized atherosclerosis, not with respect to platelet adhesion on vasculature damaged as a result of physical injury during a medical procedure. Platelet aggregation requires platelet activation which depends on the interaction between the ligand and its specific platelet surface receptor.

"Platelet activation" refers either to the change in conformation (shape) of a cell, expression of cell surface proteins (e.g., the IIb/IIIa receptor complex, loss of

GPIb surface protein), and secretion of platelet derived factors (e.g., serotonin, growth factors).

"Patient" refers to animals, preferably mammals, most preferably humans, and includes males and females, and children and adults.

"Therapeutically effective amount" refers to the amount of the compound and/or composition that is effective to achieve its intended purpose.

"Transdermal" refers to the delivery of a compound by passage through the skin and into the blood stream.

"Transmucosal" refers to delivery of a compound by passage of the compound through the mucosal tissue and into the blood stream.

"Penetration enhancement" or "permeation enhancement" refers to an increase in the permeability of the skin or mucosal tissue to a selected pharmacologically active compound such that the rate at which the compound permeates through the skin or mucosal tissue is increased.

"Carriers" or "vehicles" refers to carrier materials suitable for compound administration and include any such material known in the art such as, for example, any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is non-toxic and which does not interact with any components of the composition in a deleterious manner.

"Nitric oxide adduct" or "NO adduct" refers to compounds and functional groups which, under physiological conditions, can donate, release and/or directly or indirectly transfer any of the three redox forms of nitrogen monoxide (NO^+, NO^-, NO•), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

"Nitric oxide releasing" or "nitric oxide donating" refers to methods of donating, releasing and/or directly or indirectly transferring any of the three redox forms of nitrogen monoxide (NO^+, NO^-, NO•), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

"Nitric oxide donor" or "NO donor" refers to compounds that donate, release and/or directly or indirectly transfer a nitrogen monoxide species, and/or stimulate the endogenous production of nitric oxide or endothelium-derived relaxing factor (EDRF) *in vivo* and/or elevate endogenous levels of nitric oxide or EDRF *in vivo*. "NO donor" also includes compounds that are substrates for nitric oxide synthase.

"Alkyl" refers to a lower alkyl group, a haloalkyl group, a hydroxyalkyl group, an

alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein. An alkyl group may also comprise one or more radical species, such as, for example a cycloalkylalkyl group or a heterocyclicalkyl group.

"Lower alkyl" refers to branched or straight chain acyclic alkyl group comprising one to about ten carbon atoms (preferably one to about eight carbon atoms, more preferably one to about six carbon atoms). Exemplary lower alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, iso-amyl, hexyl, octyl, and the like.

"Substituted lower alkyl" refers to a lower alkyl group, as defined herein, wherein one or more of the hydrogen atoms have been replaced with one or more R^{100} groups, wherein each R^{100} is independently a hydroxy, an oxo, a carboxyl, a carboxamido, a halo, a cyano or an amino group, as defined herein.

"Haloalkyl" refers to a lower alkyl group, an alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein, to which is appended one or more halogens, as defined herein. Exemplary haloalkyl groups include trifluoromethyl, chloromethyl, 2-bromobutyl, 1-bromo-2-chloro-pentyl, and the like.

"Alkenyl" refers to a branched or straight chain C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) that can comprise one or more carbon-carbon double bonds. Exemplary alkenyl groups include propylenyl, buten-1-yl, isobutenyl, penten-1-yl, 2,2-methylbuten-1-yl, 3-methylbuten-1-yl, hexan-1-yl, hepten-1-yl, octen-1-yl, and the like.

"Lower alkenyl" refers to a branched or straight chain C_2-C_4 hydrocarbon that can comprise one or two carbon-carbon double bonds.

"Substituted alkenyl" refers to a branched or straight chain C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) which can comprise one or more carbon-carbon double bonds, wherein one or more of the hydrogen atoms have been replaced with one or more R^{100} groups, wherein each R^{100} is independently a hydroxy, an oxo, a carboxyl, a carboxamido, a halo, a cyano or an amino group, as defined herein.

"Alkynyl" refers to an unsaturated acyclic C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) that can comprise one or more carbon-carbon triple bonds. Exemplary alkynyl groups include ethynyl,

propynyl, butyn-1-yl, butyn-2-yl, pentyl-1-yl, pentyl-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyl-2-yl, hexyl-3-yl, 3,3-dimethyl-butyn-1-yl, and the like.

"Bridged cycloalkyl" refers to two or more cycloalkyl groups, heterocyclic groups, or a combination thereof fused via adjacent or non-adjacent atoms. Bridged cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, carboxyl, alkylcarboxylic acid, aryl, amidyl, ester, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo and nitro. Exemplary bridged cycloalkyl groups include adamantyl, decahydronapthyl, quinuclidyl, 2,6-dioxabicyclo(3.3.0)octane, 7-oxabycyclo(2.2.1)heptyl, 8-azabicyclo(3,2,1)oct-2-enyl and the like.

"Cycloalkyl" refers to a saturated or unsaturated cyclic hydrocarbon comprising from about 3 to about 10 carbon atoms. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, aryl, amidyl, ester, hydroxy, halo, carboxyl, alkylcarboxylic acid, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo, alkylsulfinyl, and nitro. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like.

"Heterocyclic ring or group" refers to a saturated or unsaturated cyclic hydrocarbon group having about 2 to about 10 carbon atoms (preferably about 4 to about 6 carbon atoms) where 1 to about 4 carbon atoms are replaced by one or more nitrogen, oxygen and/or sulfur atoms. Sulfur maybe in the thio, sulfinyl or sulfonyl oxidation state. The heterocyclic ring or group can be fused to an aromatic hydrocarbon group. Heterocyclic groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylthio, aryloxy, arylthio, arylalkyl, hydroxy, oxo, thial, halo, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, amidyl, ester, alkylcarbonyl, arylcarbonyl, alkylsulfinyl, carboxamido, alkylcarboxamido, arylcarboxamido, sulfonic acid, sulfonic ester, sulfonamido and nitro. Exemplary heterocyclic groups include pyrrolyl, furyl, thienyl, 3-pyrrolinyl,4,5,6-trihydro-2H-pyranyl, pyridinyl, 1,4-dihydropyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrhydrofuranyl, tetrazolyl, pyrrolinyl, pyrrolindinyl, oxazolindinyl 1,3-

dioxolanyl, imidazolinyl, imidazolindinyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, benzothiazolinyl, quinolinyl, and the like.

"Heterocyclic compounds" refer to mono- and polycyclic compounds comprising at least one aryl or heterocyclic ring.

"Aryl" refers to a monocyclic, bicyclic, carbocyclic or heterocyclic ring system comprising one or two aromatic rings. Exemplary aryl groups include phenyl, pyridyl, napthyl, quinoyl, tetrahydronaphthyl, furanyl, indanyl, indenyl, indoyl, and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, alkylthio, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, halo, cyano, alkylsulfinyl, hydroxy, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, alkylcarbonyl, arylcarbonyl, amidyl, ester, carboxamido, alkylcarboxamido, carbomyl, sulfonic acid, sulfonic ester, sulfonamido and nitro. Exemplary substituted aryl groups include tetrafluorophenyl, pentafluorophenyl, sulfonamide, alkylsulfonyl, arylsulfonyl, and the like.

"Cycloalkenyl" refers to an unsaturated cyclic C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) which can comprise one or more carbon-carbon triple bonds.

"Alkylaryl" refers to an alkyl group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary alkylaryl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl, and the like.

"Arylalkyl" refers to an aryl radical, as defined herein, attached to an alkyl radical, as defined herein. Exemplary arylalkyl groups include benzyl, phenylethyl, 4-hydroxybenzyl, 3-fluorobenzyl, 2-fluorophenylethyl, and the like.

"Arylalkenyl" refers to an aryl radical, as defined herein, attached to an alkenyl radical, as defined herein. Exemplary arylalkenyl groups include styryl, propenylphenyl, and the like.

"Cycloalkylalkyl" refers to a cycloalkyl radical, as defined herein, attached to an alkyl radical, as defined herein.

"Cycloalkylalkoxy" refers to a cycloalkyl radical, as defined herein, attached

to an alkoxy radical, as defined herein.

"Cycloalkylalkylthio" refers to a cycloalkyl radical, as defined herein, attached to an alkylthio radical, as defined herein.

"Heterocyclicalkyl" refers to a heterocyclic ring radical, as defined herein, attached to an alkyl radical, as defined herein.

"Arylheterocyclic ring" refers to a bi- or tricyclic ring comprised of an aryl ring, as defined herein, appended via two adjacent carbon atoms of the aryl ring to a heterocyclic ring, as defined herein. Exemplary arylheterocyclic rings include dihydroindole, 1,2,3,4-tetra-hydroquinoline, and the like.

"Alkylheterocyclic ring" refers to a heterocyclic ring radical, as defined herein, attached to an alkyl radical, as defined herein. Exemplary alkylheterocyclic rings include 2-pyridylmethyl, 1-methylpiperidin-2-one-3-methyl, and the like.

"Alkoxy" refers to $R_{50}O$-, wherein R_{50} is an alkyl group, as defined herein (preferably a lower alkyl group or a haloalkyl group, as defined herein). Exemplary alkoxy groups include methoxy, ethoxy, t-butoxy, cyclopentyloxy, trifluoromethoxy, and the like.

"Aryloxy" refers to $R_{55}O$-, wherein R_{55} is an aryl group, as defined herein. Exemplary arylkoxy groups include napthyloxy, quinolyloxy, isoquinolizinyloxy, and the like.

"Alkylthio" refers to $R_{50}S$-, wherein R_{50} is an alkyl group, as defined herein.

"Lower alkylthio" refers to a lower alkyl group, as defined herein, appended to a thio group, as defined herein.

"Arylalkoxy" or "alkoxyaryl" refers to an alkoxy group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary arylalkoxy groups include benzyloxy, phenylethoxy, chlorophenylethoxy, and the like.

"Alkoxyalkyl" refers to an alkoxy group, as defined herein, appended to an alkyl group, as defined herein. Exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, isopropoxymethyl, and the like.

"Alkoxyhaloalkyl" refers to an alkoxy group, as defined herein, appended to a haloalkyl group, as defined herein. Exemplary alkoxyhaloalkyl groups include 4-methoxy-2-chlorobutyl and the like.

"Cycloalkoxy" refers to $R_{54}O$-, wherein R_{54} is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkoxy groups include cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

"Cycloalkylthio" refers to $R_{54}S$-, wherein R_{54} is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkylthio groups include cyclopropylthio, cyclopentylthio, cyclohexylthio, and the like.

"Haloalkoxy" refers to an alkoxy group, as defined herein, in which one or more of the hydrogen atoms on the alkoxy group are substituted with halogens, as defined herein. Exemplary haloalkoxy groups include 1,1,1-trichloroethoxy, 2-bromobutoxy, and the like.

"Hydroxy" refers to -OH.

"Oxo " refers to =O.

"Oxy " refers to $-O^- R_{77}^+$ wherein R_{77} is an organic or inorganic cation.

"Oxime" refers to $=N-OR_{81}$ wherein $R_{81}$is a hydrogen, an alkyl group, an aryl group, an alkylsulfonyl group, an arylsulfonyl group, a carboxylic ester, an alkylcarbonyl group, an arylcarbonyl group, a carboxamido group, an alkoxyalkyl group or an alkoxyaryl group.

"Hydrazone refers to $=N-N(R_{81})(R'_{81})$ wherein R'_{81} is independently selected from R_{81}, and R_{81} is as defined herein.

"Organic cation" refers to a positively charged organic ion. Exemplary organic cations include alkyl substituted ammonium cations, and the like.

"Inorganic cation" refers to a positively charged metal ion. Exemplary inorganic cations include Group I metal cations such as for example, sodium, potassium, and the like.

"Hydroxyalkyl" refers to a hydroxy group, as defined herein, appended to an alkyl group, as defined herein.

"Nitrate" refers to $-O-NO_2$.

"Nitrite" refers to -O-NO.

"Thionitrate" refers to $-S-NO_2$.

"Thionitrite" and "nitrosothiol" refer to -S-NO.

"Nitro" refers to the group $-NO_2$ and "nitrosated" refers to compounds that have been substituted therewith.

"Nitroso" refers to the group -NO and "nitrosylated" refers to compounds that have been substituted therewith.

"Nitrile" and "cyano" refer to -CN.

"Halogen" or "halo" refers to iodine (I), bromine (Br), chlorine (Cl), and/or fluorine (F).

"Amino " refers to -NH_2, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein.

"Alkylamino" refers to $R_{50}NH$-, wherein R_{50} is an alkyl group, as defined herein. Exemplary alkylamino groups include methylamino, ethylamino, butylamino, cyclohexylamino, and the like.

"Arylamino" refers to $R_{55}NH$-, wherein R_{55} is an aryl group, as defined herein.

"Dialkylamino" refers to $R_{52}R_{53}N$-, wherein R_{52} and R_{53} are each independently an alkyl group, as defined herein. Exemplary dialkylamino groups include dimethylamino, diethylamino, methyl propargylamino, and the like.

"Diarylamino" refers to $R_{55}R_{60}N$-, wherein R_{55} and R_{60} are each independently an aryl group, as defined herein.

"Alkylarylamino or arylalkylamino" refers to $R_{52}R_{55}N$-, wherein R_{52} is an alkyl group, as defined herein, and R_{55} is an aryl group, as defined herein.

"Alkylarylalkylamino " refers to $R_{52}R_{79}N$-, wherein R_{52} is an alkyl group, as defined herein, and R_{79} is an arylalkyl group, as defined herein.

"Alkylcycloalkylamino " refers to $R_{52}R_{80}N$-, wherein R_{52} is an alkyl group, as defined herein, and R_{80} is an cycloalkyl group, as defined herein.

"Aminoalkyl " refers to an amino group, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein, to which is appended an alkyl group, as defined herein. Exemplary aminoalkyl groups include dimethylaminopropyl, diphenylaminocyclopentyl, methylaminomethyl, and the like.

"Aminoaryl " refers to an aryl group to which is appended an alkylamino group, a arylamino group or an arylalkylamino group. Exemplary aminoaryl groups include anilino, N-methylanilino, N-benzylanilino, and the like.

"Thio" refers to –S-.

"Sulfinyl" refers to -S(O)-.

"Methanthial" refers to -C(S)-.

"Thial" refers to =S.

"Sulfonyl" refers to -$S(O)_2$-.

"Sulfonic acid" refers to -$S(O)_2OR_{76}$, wherein R_{76} is a hydrogen, an organic cation or an inorganic cation, as defined herein.

"Alkylsulfonic acid" refers to a sulfonic acid group, as defined herein,

appended to an alkyl group, as defined herein.

"Arylsulfonic acid" refers to a sulfonic acid group, as defined herein, appended to an aryl group, as defined herein

"Sulfonic ester" refers to $-S(O)_2OR_{58}$, wherein R_{58} is an alkyl group, an aryl group, or an aryl heterocyclic ring, as defined herein.

"Sulfonamido" refers to $-S(O)_2-N(R_{51})(R_{57})$, wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Alkylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an alkyl group, as defined herein.

"Arylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an aryl group, as defined herein.

"Alkylthio" refers to $R_{50}S-$, wherein R_{50} is an alkyl group, as defined herein (preferably a lower alkyl group, as defined herein).

"Arylthio" refers to $R_{55}S-$, wherein R_{55} is an aryl group, as defined herein.

"Arylalkylthio" refers to an aryl group, as defined herein, appended to an alkylthio group, as defined herein.

"Alkylsulfinyl" refers to $R_{50}-S(O)-$, wherein R_{50} is an alkyl group, as defined herein.

"Alkylsulfonyl" refers to $R_{50}-S(O)_2-$, wherein R_{50} is an alkyl group, as defined herein.

"Alkylsulfonyloxy" refers to $R_{50}-S(O)_2-O-$, wherein R_{50} is an alkyl group, as defined herein.

"Arylsulfinyl" refers to $R_{55}-S(O)-$, wherein R_{55} is an aryl group, as defined herein.

"Arylsulfonyl" refers to $R_{55}-S(O)_2-$, wherein R_{55} is an aryl group, as defined herein.

"Arylsulfonyloxy" refers to $R_{55}-S(O)_2-O-$, wherein R_{55} is an aryl group, as defined herein.

"Amidyl" refers to $R_{51}C(O)N(R_{57})-$ wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein.

"Ester" refers to $R_{51}C(O)O-$ wherein R_{51} is a hydrogen atom, an alkyl group,

an aryl group or an arylheterocyclic ring, as defined herein.

"Carbamoyl" refers to -O-C(O)N(R_{51})(R_{57}), wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Carboxyl" refers to –C(O)OR_{76}, wherein R_{76} is a hydrogen, an organic cation or an inorganic cation, as defined herein.

"Carbonyl" refers to –C(O)-.

"Alkylcarbonyl" refers to R_{52}-C(O)-, wherein R_{52} is an alkyl group, as defined herein.

"Arylcarbonyl" refers to R_{55}-C(O)-, wherein R_{55} is an aryl group, as defined herein.

"Arylalkylcarbonyl" refers to R_{55}-R_{52}-C(O)-, wherein R_{55} is an aryl group, as defined herein, and R_{52} is an alkyl group, as defined herein.

"Alkylarylcarbonyl" refers to R_{52}-R_{55}-C(O)-, wherein R_{55} is an aryl group, as defined herein, and R_{52} is an alkyl group, as defined herein.

"Heterocyclicalkylcarbonyl" refer to R_{78}C(O)- wherein R_{78} is a heterocyclicalkyl group, as defined herein.

"Carboxylic ester" refers to -C(O)OR_{58}, wherein R_{58} is an alkyl group, an aryl group or an aryl heterocyclic ring, as defined herein.

"Alkylcarboxylic acid" and "alkylcarboxyl" refer to an alkyl group, as defined herein, appended to a carboxyl group, as defined herein.

"Alkylcarboxylic ester" refers to an alkyl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Arylcarboxylic acid" refers to an aryl group, as defined herein, appended to a carboxyl group, as defined herein.

"Arylcarboxylic ester" and "arylcarboxyl" refer to an aryl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Carboxamido" refers to -C(O)N(R_{51})(R_{57}), wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Alkylcarboxamido" refers to an alkyl group, as defined herein, appended to a carboxamido group, as defined herein.

"Arylcarboxamido" refers to an aryl group, as defined herein, appended to a carboxamido group, as defined herein.

"Urea" refers to -N(R_{59})-C(O)N(R_{51})(R_{57}) wherein R_{51}, R_{57}, and R_{59} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Phosphoryl" refers to -P(R_{70})(R_{71})(R_{72}), wherein R_{70} is a lone pair of electrons, thial or oxo, and R_{71} and R_{72} are each independently a covalent bond, a hydrogen, a lower alkyl, an alkoxy, an alkylamino, a hydroxy, an oxy or an aryl, as defined herein.

"Silyl" refers to -Si(R_{73})(R_{74})(R_{75}), wherein R_{73}, R_{74} and R_{75} are each independently a covalent bond, a lower alkyl, an alkoxy, an aryl or an arylalkoxy, as defined herein.

Compounds that donate, transfer or release nitric oxide species *in vivo* have been recognized as having a wide spectrum of advantages and applications. The invention is based on the unexpected discovery of the effects of such compounds alone and together with one or more COX inhibitors. Treatment or prevention of cyclooxygenase-3 mediated diseases and/or disorders can be obtained by the use of COX inhibitors; or by the use of COX inhibitors in conjunction with one or more compounds that donate, release or transfer nitric oxide and/or stimulate endogenous production of NO and/or EDRF *in vivo* and/or is a substrate for nitric oxide synthase, and, with one or more therapeutic agents.

Suitable cyclooxygenase-2 selective inhibitors for use in the invention, include, but are not limited to, those disclosed in, for example, U. S. Patent Nos. 3,196,162, 3,271,416, 5,134,142, 5,344,991, 5,360,925, 5,380,738, 5,393,790, 5,409,944, 5,434,178, 5,436,265, 5,466,823, 5,474,995, 5,475,021, 5,480,999, 5,486,534, 5,504,215, 5,508,426, 5,510,368, 5,510,496, 5,516,907, 5,521,207, 5,521,213, 5,536,752, 5,466,823, 5,550,142, 5,550,147, 5,552,422, 5,580,985, 5,585,504, 5,593,994, 5,604,253, 5,604,260, 5,563,165, 5,616,601, 5,620,999, 5,633,272, 5,639,780, 5,670,533, 5,677,318, 5,668,161, 5,681,842, 5,686,460, 5,686,470, 5,691,374, 5,696,143, 5,698,584, 5,700,816, 5,710,140, 5,719, 163, 5,733,909, 5,750,558, 5,753,688, 5,756,530, 5,756,531, 5,760,068, 5,776,967, 5,776,984, 5,783,597, 5,789,413, 5,807,873, 5,817,700, 5,824,699, 5,830,911, 5,840,746, 5,840,924, 5,849,943 5,859,257, 5,861,419, 5,870,973, 5,883,267,

5,905,089, 5,908,852, 5,908,858, 5,925,631, 5,932,586, 5,935,990, 5,945,539, 5,968,958, 5,972,986, 5,980,905, 5,981,576, 5,985,902, 5,990,148, 5,994,379, 5,994,381, 6,001,843, 6,020,343, 6,025,353, 6,028,072, 6,040,319, 6,046,217, 6,071,954, 6,077,869, 6,080,876, 6,083,969, 6,136,839, 6,169,188, 6,232,315, 6,245,797, 6,248,745, 6,300,363, 6,306,842, 6,342,510, 6,355,680, and in WO 91/19708, WO 94/03378, WO 94/13635, WO 94/15723, WO 94/15932, WO 94/20480, WO 94/26731, WO 94/27980, WO 95/00501, WO 95/11883, WO 95/15315, WO 95/15316, WO 95/15317, WO 95/15318, WO 95/18799, WO 95/21817, WO 95/30652, WO 96/30656, WO 96/03387, WO 96/03388, WO 96/03392, WO 96/03385, WO 96/03387, WO 96/03388, WO 96/03392, WO 96/06840, WO 96/09293, WO 96/09304, WO 96/10012, WO 96/13483, WO 96/16934, WO 96/19462, WO 96/19463, WO 96/19469, WO 96/21667, WO 96/23786, WO 96/25405, WO 96/24584, WO 96/24585, WO 96/26921, WO 96/31509, WO 96/36617, WO 96/36623, WO 96/37467, WO 96/37438, WO 96/37496, WO 96/38442, WO 96/41626, WO 96/41645, WO 97/03953, WO 97/09977, WO 97/11704, WO 97/13755, WO 97/13767, WO 97/14691, WO 97/16435, WO 97/25045, WO 97/27181, WO 97/28120, WO 97/28121, WO 97/29776, WO 97/34882, WO 97/36863, WO 97/37984, WO 97/38986, WO 97/40012, WO 97/41100, WO 97/44027, WO 97/45420, WO 98/00416, WO 98/03484, WO 98/04527, WO 98/05639, WO 98/06708. WO 98/07714, WO 98/11080, WO 98/21195, WO 98/22422, WO 98/24584, WO 98/32732, WO 98/33769, WO 98/39330, WO 98/41511, WO 98/41516, WO 98/43648, WO 98/43966, WO 98/46594, WO 98/37509, WO 98/47871, WO 98/47890, WO 98/50033, WO 98/50075, WO 98/52937, WO 98/57910, WO 98/57924, WO 99/05104, WO 99/10331, WO 99/10332, WO 99/11605, WO 99/12930, WO 99/13799, WO 99/14194, WO 99/14195, WO 99/14205, WO 99/15503, WO 99/15505, WO 99/15531, WO 99/18960, WO 99/20110, WO 99/21585, WO 99/22720, WO 99/23087, WO 99/25382, WO 99/25695, WO 99/33796, WO 99/35130, WO 99/41224, WO 99/45913, WO 99/55830, WO 99/59634, WO 99/59635, WO 99/61016, WO 99/61436, WO 99/62884, WO 99/64415, WO 00/00200, WO 00/01380, WO 00/08024, , WO 00/10012, WO 00/10993, WO 00/13685, WO 00/18352, WO 00/23433, WO 00/24719, WO 00/25779, WO 00/26216, WO 00/27382, WO 00/27394, WO 00/29022, WO 00/29023, WO 00/37107, WO 00/38716, WO 00/38730, WO 00/38786, WO 00/48583, WO

00/516585, WO 00/52008, WO 00/53149, WO 00/66562, WO 00/68215, WO 00/73278, WO 01/15686, WO 01/23346, WO 01/45703, WO 01/45698, WO 01/54688, WO 01/56555, WO 01/56573, WO 01/81332, WO 01/87343, WO 02/20090 and WO 02/060378; and in PCT Application Nos. PCT/US03/18052, PCT/US03/19850, PCT/US03/20421 and PCT/US03/23605, and in EP 0 087 629 B1, EP 0 418 845 B1, EP 0 554 829 A2, EP 0 745 596 A1, EP 0 788 476 B1, EP 0 863 134 A1, EP 0 882 016 B1, EP 0 937 722 A1, EP 0 985,665, EP 1 006 114 A1, EP 1 104 759 A1, EP 1 104 760; and in U.S. Patent Application Nos. 10/102,865, 10/024,046, 10/603,098, 10/608,333, 10/628,375 and 60/387,433; and in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry; the disclosures of each of which are incorporated by reference herein in their entirety. Exemplary cyclooxygenase-2 selective inhibitors, include, but are not limited to, NS-386, nimesulide, flosulide, celecoxib, rofecoxib, COX-189, etoracoxib, Bextra, Dynastat, Arcoxia, SC-57666, DuP 697, SC-58125, SC-58635, and the like.

The COX inhibitor compounds can be nitrosated and/or nitrosylated through one or more sites such as oxygen, sulfur and/or nitrogen using the methods described in the examples herein and using conventional methods known to one skilled in the art. For example, known methods for nitrosating and/or nitrosylating compounds are described in U.S. Patent Nos. 5,380,758, 5,859,053, 5,703,073 and 6,297,260; and in WO 94/03421, WO 94/04484, WO 94/12463, WO 95/09831, WO 95/19952, WO 95/30641, WO 97/27749, WO 98/19672, WO 98/21193, WO 00/51988, WO 00/61604, WO 00/72838, WO 01/00563, WO 01/04082, WO 01/10814, WO 01/12584, WO 01/45703, WO 00/61541, WO 00/61537, WO 02/11707, WO 02/30866 and in Oae et al, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety. The methods of nitrosating and/or nitrosylating the compounds described in the examples herein and in these references can be applied by one skilled in the art to produce any of the nitrosated and/or nitrosylated COX-2 inhibitors described herein.

Suitable nitrosated and/or nitrosylated cyclooxygenase inhibitors, include, but are not limited to, those disclosed in, for example, WO 01/45703 and WO 02/60378, and in U.S. Patent Application Nos. 10/102,865, 10/024,046, 10/603,098, 10/608,333, 10/628,375 and 60/387,433; the disclosures of each of which are incorporated by

reference herein in their entirety.

Suitable NSAIDs include, but are not limited to, acetaminophen, acemetacin, aceclofenac, alminoprofen, amfenac, bendazac, benoxaprofen, bromfenac, bucloxic acid, butibufen, carprofen, cinmetacin, clopirac, diclofenac, etodolac, felbinac, fenclozic acid, fenbufen, fenoprofen, fentiazac, flunoxaprofen, flurbiprofen, ibufenac, ibuprofen, indomethacin, isofezolac, isoxepac, indoprofen, ketoprofen, lonazolac, loxoprofen, metiazinic acid, mofezolac, miroprofen, naproxen, oxaprozin, pirozolac, pirprofen, pranoprofen, protizinic acid, salicylamide, sulindac, suprofen, suxibuzone, tiaprofenic acid, tolmetin, xenbucin, ximoprofen, zaltoprofen, zomepirac, aspirin, acemetcin, bumadizon, carprofenac, clidanac, diflunisal, enfenamic acid, fendosal, flufenamic acid, flunixin, gentisic acid, ketorolac, meclofenamic acid, mefenamic acid, mesalamine, prodrugs thereof, and the like. Suitable NSAIDs are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; the Merck Index on CD-ROM, 13th Edition; and in U.S. Patent Nos. 6,057,347 and 6,297,260 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety. Suitable nitrosated and/or nitrosylated NSAIDs include, but are not limited to, those disclosed in, for example, U U.S. Patent Nos. 5,380,758, 5,621,000, 5,700,947, 5,780,495, 5,859,053, 5,703,073, 6,297,260, 6,429,223 and 6,355,666; and in WO 94/03421, WO 94/04484, WO 94/12463, WO 95/09831, WO 95/30641, WO 97/16405, WO 97/27749, WO 98/09948, WO 98/19672, WO 98/25918, WO 01/00563, WO 00/44705, WO 00/51988, WO 00/61537, WO 00/61541, WO 01/12584, WO 01/66088, WO 00/72838, WO 01/04082, WO 01/10814, WO 01/45703, WO 02/11706, WO 02/11707, WO 02/00167 and WO 02/30866; and in U.S. Application No. 10/612,014; the disclosures of each of which are incorporated by reference herein in their entirety.

The compounds of the invention include the COX-2 inhibitors, including those described herein, which have been nitrosated and/or nitrosylated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen. The nitrosated and/or nitrosylated COX inhibitors of the invention donate, transfer or release a biologically active form of nitrogen monoxide (i.e., nitric oxide).

Nitrogen monoxide can exist in three forms: NO- (nitroxyl), NO• (uncharged nitric oxide) and NO^+ (nitrosonium). NO• is a highly reactive short-lived species that

is potentially toxic to cells. This is critical because the pharmacological efficacy of NO depends upon the form in which it is delivered. In contrast to the nitric oxide radical (NO•), nitrosonium (NO^+) does not react with O_2 or O_2^- species, and functionalities capable of transferring and/or releasing NO^+ and NO- are also resistant to decomposition in the presence of many redox metals. Consequently, administration of charged NO equivalents (positive and/or negative) is a more effective means of delivering a biologically active NO to the desired site of action.

Compounds contemplated for use in the invention, e.g., COX inhibitor, that can be optionally nitrosated and/or nitrosylated, through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfhydryl condensation) and/or nitrogen, are, optionally, used in combination with nitric oxide and compounds that release nitric oxide or otherwise directly or indirectly deliver or transfer a biologically active form of nitrogen monoxide to a site of its intended activity, such as on a cell membrane *in vivo*.

The term "nitric oxide" encompasses uncharged nitric oxide (NO•) and charged nitrogen monoxide species, preferably charged nitrogen monoxide species, such as nitrosonium ion (NO^+) and nitroxyl ion (NO-). The reactive form of nitric oxide can be provided by gaseous nitric oxide. The nitrogen monoxide releasing, delivering or transferring compounds have the structure F-NO, wherein F is a nitrogen monoxide releasing, delivering or transferring moiety, and include any and all such compounds which provide nitrogen monoxide to its intended site of action in a form active for its intended purpose. The term "NO adducts" encompasses any nitrogen monoxide releasing, delivering or transferring compounds, including, for example, S-nitrosothiols, nitrites, nitrates, S-nitrothiols, sydnonimines, 2-hydroxy-2-nitrosohydrazines, (NONOates), (E)-alkyl-2-((E)- hydroxyimino)-5-nitro-3-hexeneamide (FK-409), (E)-alkyl-2-((E)-hydroxyimino)-5-nitro-3- hexeneamines, N-((2Z, 3E)-4-ethyl-2-(hydroxyimino)-6-methyl-5-nitro-3-heptenyl)-3-pyridinecarboxamide (FR 146801), nitrosoamines, furoxans as well as substrates for the endogenous enzymes which synthesize nitric oxide. NONOates include, but are not limited to, (Z)-1-(N-methyl-N-(6-(N-methyl-ammoniohexyl)amino))diazen-1-ium-1,2-diolate ("MAHMA/NO"), (Z)-1-(N-(3-ammoniopropyl)-N-(n-propyl)amino)diazen-1-ium-1,2-diolate ("PAPA/NO"), (Z)-1-(N-(3-aminopropyl)-N-(4-(3-aminopropylammonio)butyl)-amino) diazen-1-ium-1,2-diolate (spermine NONOate or "SPER/NO") and sodium(Z)-1-(N,N- diethylamino)diazenium-1,2-

diolate (diethylamine NONOate or "DEA/NO") and derivatives thereof. NONOates are also described in U.S. Patent Nos. 6,232,336, 5,910,316 and 5,650,447, the disclosures of which are incorporated herein by reference in their entirety. The "NO adducts" can be mono-nitrosylated, poly-nitrosylated, mono-nitrosated and/or poly-nitrosated at a variety of naturally susceptible or artificially provided binding sites for biologically active forms of nitrogen monoxide.

One group of NO adducts is the S-nitrosothiols, which are compounds that include at least one -S-NO group. These compounds include S-nitroso-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); S-nitrosylated amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures and derivatives thereof); S-nitrosylated sugars; S-nitrosylated, modified and unmodified, oligonucleotides (preferably of at least 5, and more preferably 5-200 nucleotides); straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted S-nitrosylated hydrocarbons; and S-nitroso heterocyclic compounds. S-nitrosothiols and methods for preparing them are described in U.S. Patent Nos. 5,380,758 and 5,703,073; WO 97/27749; WO 98/19672; and Oae et al, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety.

Another embodiment of the invention is S-nitroso amino acids where the nitroso group is linked to a sulfur group of a sulfur-containing amino acid or derivative thereof. Such compounds include, for example, S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione, S-nitroso-cysteinyl-glycine, and the like.

Suitable S-nitrosylated proteins include thiol-containing proteins (where the NO group is attached to one or more sulfur groups on an amino acid or amino acid derivative thereof) from various functional classes including enzymes, such as tissue-type plasminogen activator (TPA) and cathepsin B; transport proteins, such as lipoproteins; heme proteins, such as hemoglobin and serum albumin; and biologically protective proteins, such as immunoglobulins, antibodies and cytokines. Such nitrosylated proteins are described in WO 93/09806, the disclosure of which is incorporated by reference herein in its entirety. Examples include polynitrosylated albumin where one or more thiol or other nucleophilic centers in the protein are modified.

Other examples of suitable S-nitrosothiols include:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring. a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, an arylsulfonyloxy, a urea, a nitro, -T-Q'-, or $-(C(R_g)(R_h))_k\text{-}T\text{-}Q'$ or R_e and R_f taken together are an oxo, a methanthial, a heterocyclic ring, a cycloalkyl group, an oxime, a hydrazone or a bridged cycloalkyl group; Q' is -NO or $-NO_2$; and T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyloxy, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, $-CH_2\text{-}C(T\text{-}Q')(R_g)(R_h)$, or $-(N_2O_2-)^-\bullet M^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-CH_2\text{-}C(T\text{-}Q')(R_g)(R_h)$ or $-(N_2O_2-)\bullet M^+$; then "-T-Q'" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group; and

R_g and R_h at each occurrence are independently R_e;

In cases where R_e and R_f are a heterocyclic ring or taken together R_e and R_f are a heterocyclic ring, then R_i can be a substituent on any disubstituted nitrogen contained within the radical wherein R_i is as defined herein.

Nitrosothiols can be prepared by various methods of synthesis. In general, the

thiol precursor is prepared first, then converted to the S-nitrosothiol derivative by nitrosation of the thiol group with $NaNO_2$ under acidic conditions (pH is about 2.5) which yields the S-nitroso derivative. Acids which can be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. The thiol precursor can also be nitrosylated by reaction with an organic nitrite such as tert-butyl nitrite, or a nitrosonium salt such as nitrosonium tetrafluoroborate in an inert solvent.

Another group of NO adducts for use in the invention, where the NO adduct is a compound that donates, transfers or releases nitric oxide, include compounds comprising at least one ON-O- or ON-N- group. The compounds that include at least one ON-O- or ON-N- group are preferably ON-O- or ON-N-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); ON-O- or ON-N-amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); ON-O- or ON-N-sugars; ON-O- or -ON-N- modified or unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); ON-O- or ON-N- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and ON-O-, ON-N- or ON-C-heterocyclic compounds.

Another group of NO adducts for use in the invention include nitrates that donate, transfer or release nitric oxide, such as compounds comprising at least one O_2N-O-,

O_2N-N- or O_2N-S- group. Preferred among these compounds are O_2N-O-, O_2N-N- or O_2N-S- polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); O_2N-O-, O_2N-N- or

O_2N-S- amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); O_2N-O-, O_2N-N- or O_2N-S- sugars; O_2N-O-, O_2N-N- or O_2N-S- modified and unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); O_2N-O-, O_2N-N- or O_2N-S- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and O_2N-O-, O_2N-N- or O_2N-S- heterocyclic compounds. Preferred examples of compounds comprising at least one O_2N-O-, O_2N-N- or O_2N-S- group include isosorbide dinitrate, isosorbide mononitrate, clonitrate, erythrityl tetranitrate, mannitol hexanitrate, nitroglycerin, pentaerythritoltetranitrate, pentrinitrol,

propatylnitrate and organic nitrates with a sulfhydryl-containing amino acid such as, for example SPM 3672, SPM 5185, SPM 5186 and those disclosed in U. S. Patent Nos. 5,284,872, 5,428,061, 5,661,129, 5,807,847 and 5,883,122 and in WO 97/46521, WO 00/54756 and in WO 03/013432, the disclosures of each of which are incorporated by reference herein in their entirety.

Another group of NO adducts are N-oxo-N-nitrosoamines that donate, transfer or release nitric oxide and are represented by the formula: $R^{1"}R^{2"}N\text{-}N(O\text{-}M^{+})\text{-}NO$, where $R^{1"}$ and $R^{2"}$ are each independently a polypeptide, an amino acid, a sugar, a modified or unmodified oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and where M^{+} is an organic or inorganic cation, such as, for example, an alkyl substituted ammonium cation or a Group I metal cation.

The invention is also directed to compounds that stimulate endogenous NO or elevate levels of endogenous endothelium-derived relaxing factor (EDRF) *in vivo* or are substrates for nitric oxide synthase. Such compounds include, for example, L-arginine, L-homoarginine, and N-hydroxy-L-arginine, including their nitrosated and nitrosylated analogs (e.g., nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated L-homoarginine and nitrosylated L-homoarginine), precursors of L-arginine and/or physiologically acceptable salts thereof, including, for example, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids, inhibitors of the enzyme arginase (e.g., N-hydroxy-L-arginine and 2(S)-amino-6-boronohexanoic acid), nitric oxide mediators and/or physiologically acceptable salts thereof, including, for example, pyruvate, pyruvate precursors, α-keto acids having four or more carbon atoms, precursors of α-keto acids having four or more carbon atoms (as disclosed in WO 03/017996, the disclosure of which is incorporated herein in its entirety), and the substrates for nitric oxide synthase, cytokines, adenosin, bradykinin, calreticulin, bisacodyl, and phenolphthalein. EDRF is a vascular relaxing factor secreted by the endothelium, and has been identified as nitric oxide (NO) or a closely related derivative thereof (Palmer et al, *Nature*, 327:524-526 (1987); Ignarro et al, *Proc. Natl. Acad. Sci. USA*, 84:9265-9269 (1987)).

The invention is also based on the discovery that compounds and compositions of the invention may be used in conjunction with other therapeutic agents for co-therapies, partially or completely, in place of other conventional antiinflammatory

compounds, such as, for example, together with steroids, NSAIDs, 5-lipoxygenase (5-LO) inhibitors, leukotriene B_4 (LTB_4) receptor antagonists, leukotriene A_4 (LTA_4) hydrolase inhibitors, 5-HT agonists, HMG-CoA inhibitors, H_2 receptor antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opiods, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and mixtures of two or more thereof.

Leukotriene A_4 (LTA_4) hydrolase inhibitors refer to compounds that selectively inhibit leukotriene A_4 hydrolase with an IC_{50} of less than about 10μM, and preferably with an IC_{50} of less than about 1 μM. Suitable LTA_4 hydrolase inhibitors include, but are not limited to, RP-64966, (S,S)-3-amino-4-(4-benzyloxyphenyl)-2-hydroxybutyric acid benzyl ester, N-(2(R)-(cyclohexylmethyl)-3-(hydroxycarbamoyl)propionyl)-L-alanine, 7-(4-(4-ureidobenzyl)phenyl) heptanoic acid and 3 (3-(1E,3E-tetradecadienyl)-2-oxiranyl)benzoic acid lithium salt, and mixtures of two or more thereof.

Suitable LTB_4 receptor antagonists include, but are not limited to, ebselen, linazolast, ontazolast; WAY 121006; Bay-x-1005; BI-RM-270; CGS-25019C; ETH-615; MAFP; TMK-688; T-0757; LY 213024, LY 210073, LY 223982, LY 233469, LY 255283, LY 264086, LY 292728 and LY 293111; ONO-LB457, ONO-4057, and ONO-LB-448, S-2474, calcitrol; PF 10042; Pfizer 105696; RP 66153; SC-53228, SC-41930, SC-50605, SC-51146 and SC-53228; SB-201146 and SB-209247; SKF-104493; SM 15178; TMK-688; BPC 15, and mixtures of two or more thereof. The preferred LTB_4 receptor antagonists are calcitrol, ebselen, Bay-x-1005, CGS-25019C, ETH-615, LY-293111, ONO-4057 and TMK-688, and mixtures of two or more thereof.

Suitable 5-LO inhibitors include, but are not limited to, A-76745, 78773 and ABT761; Bay-x-1005; CMI-392; E-3040; EF-40; F-1322; ML-3000; PF-5901; R-840; rilopirox, flobufen, linasolast, lonapolene, masoprocol, ontasolast, tenidap, zileuton, pranlukast, tepoxalin, rilopirox, flezelastine hydrochloride, enazadrem phosphate, and bunaprolast, and mixtures of two or more thereof. Suitable 5-LO inhibitors are also described more fully in WO 97/29776, the disclosure of which is incorporated herein by reference in its entirety

Suitable 5-HT agonists, include, but are not limited to, rizatriptan, sumatriptan, naratriptan, zolmitroptan, eleptriptan, almotriptan, ergot alkaloids. ALX 1323, Merck

L 741604 SB 220453 and LAS 31416. Suitable 5-HT agonists are described more fully in WO 0025779, and in WO 00/48583. 5-HT agonists refers to a compound that is an agonist to any 5-HT receptor, including but not limited to, 5-HT_1 agonists, 5-HT_{1B} agonists and 5-HT_{1D} agonists, and the like.

Suitable steroids, include, but are not limited to, budesonide, dexamethasone, corticosterone, prednisolone, and the like. Suitable steroids are described more fully in the literature, such as in the Merck Index on CD-ROM, 13th Edition.

Suitable HMG CoA inhibitors, include, but are not limited to, reductase and synthase inhibitors, such as, for example, squalene synthetase inhibitors, benzodiazepine squalene synthase inhibitors, squalene epoxidase inhibitors, acyl-coenzyme A, bile acid sequestrants, cholesterol absorption inhibitors, and the like. Suitable HMG CoA inhibitors include simvastatin, pravastatin, lovastatin, mevastatin, fluvastatin, atorvastatin, cerivastatin, and the like, and are described more fully in U.S. Patent No. 6,245,797 and WO 99/20110, the disclosures of which are incorporated herein by reference in their entirety.

Suitable NSAIDs include, but are not limited to, acetaminophen, acemetacin, aceclofenac, alminoprofen, amfenac, bendazac, benoxaprofen, bromfenac, bucloxic acid, butibufen, carprofen, cinmetacin, clopirac, diclofenac, etodolac, felbinac, fenclozic acid, fenbufen, fenoprofen, fentiazac, flunoxaprofen, flurbiprofen, ibufenac, ibuprofen, indomethacin, isofezolac, isoxepac, indoprofen, ketoprofen, lonazolac, loxoprofen, metiazinic acid, mofezolac, miroprofen, naproxen, oxaprozin, pirozolac, pirprofen, pranoprofen, protizinic acid, salicylamide, sulindac, suprofen, suxibuzone, tiaprofenic acid, tolmetin, xenbucin, ximoprofen, zaltoprofen, zomepirac, aspirin, acemetcin, bumadizon, carprofenac, clidanac, diflunisal, enfenamic acid, fendosal, flufenamic acid, flunixin, gentisic acid, ketorolac, meclofenamic acid, mefenamic acid, mesalamine, prodrugs thereof, and the like. Suitable NSAIDs are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 617-657; the Merck Index on CD-ROM, 13th Edition; and in U.S. Patent Nos. 6,057,347 and 6,297,260 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

Suitable H_2 receptor anatgonists include, but are not limited to, burimamide, cimetidine, ebrotidin, famotidine, nizatidine, roxatidine, rantidine, tiotidine, and the like. Suitable H_2 receptor antagonists are described more fully in the literature, such

as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 901-915; the Merck Index on CD-ROM, 13th Edition; and in WO 00/28988 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

Suitable antineoplastic agents, include but are not limited to, 5-FU-fibrinogen, acanthifolic acid, aminothiadiazole, altretamine, anaxirone, aclarubicin and the like. Suitable antineoplastic agents are also described in U. S. Patent No. 6,025,353 and WO 00/38730, the disclosures of which are incorporated herein by reference in their entirety.

Suitable antiplatelet agents, include but are not limited to, aspirin, ticlopidine, dipyridamole, clopidogrel, glycoprotein IIb/IIIa receptor antagonists, and the like. Suitable antineoplastic agents are also described in WO 99/45913, the disclosure of which is incorporated herein by reference in its entirety. In a preferred embodiment of the invention, the antiplatelet agent is aspirin, more preferably, low-dose aspirin (i.e. 75 mg – 100 mg/day).

Suitable thrombin inhibitors, include but are not limited to, N'-((1-(aminoiminomethyl)-4-piperidinyl)methyl)-N-(3,3-diphenylpropinyl)-L-proline amide),3-(2-phenylethylamino)-6-methyl-1-(2-amino-6-methyl-5-methylene-carboxamidomethylpyridinyl)-2-pyrazinone, 3-(2-phenethylamino)-6-methyl-1-(2-amino-6-methyl-5- methylenecarboxamidomethylpyridinyl)-2-pyridinone, and the like. Suitable thrombin inhibitors are also described in WO 00/18352, the disclosure of which is incorporated herein by reference in its entirety.

Suitable thromboxane inhibitors, include but are not limited to thromboxane synthase inhibitors, thromboxane receptor antagonists, and the like. Suitable thromboxane inhibitors, are also described in WO 01/87343, the disclosure of which is incorporated herein by reference in its entirety.

Suitable decongestants include, but are not limited to, phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine, and the like.

Suitable antitussives include, but are not limited to, codeine, hydrocodone, caramiphen, carbetapentane, dextramethorphan, and the like.

Suitable proton pump inhibitors include, but are not limited to, omeprazole, lansoprazole, pantoprazole, rabeprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, esomeprazole, 2-(2-benzimidazolyl)-pyridine, tricyclic imidazole,

thienopydidine benzimidazole, fluoroalkoxy substituted benzimidazole, dialkoxy benzimidazole, N-substituted 2-(pyridylalkenesulfinyl) benzimidazole, cycloheptenepyridine, 5-pyrrolyl-2-pyridylmethylsulfinyl benzimidazole, alkylsulfinyl benzimidazole, fluoro-pyridylmethylsulfinyl benzimidazole, imidazo[4,5-b]pydridine, RO 18-5362, IY 81149, 4-amino-3-carbonyl quinoline, 4-amino-3-acylnaphthyride, 4-aminoquinoline, 4-amino-3-acylquinoline, 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline, quinazoline, tetrahydroisoquinolin-2-yl pyrimidine, YH 1885, 3-substituted 1,2,4-thiadiazolo[4,5-a] benzimidazole, 3-substituted imidazo[1,2-d]-thiadiazole, 2-sulfinylnicotinamide, pyridylsulfinylbenz imidazole, pyridylsulfinyl thieno imidazole, theinoimidazole-toluidine, 4,5-dihydrooxazole, thienoimidazole-toluidine, Hoe-731, imidazo[1,2-a]pyridine, pyrrolo[2,3-b]pyridine,.and the like. Suitable proton pump inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; the Merck Index on CD-ROM, 13th Edition; and in WO 00/50037 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

Suitable diuretics include but are not limited to, thiazides (such as, for example, althiazide, bendroflumethiazide, benzclortriazide, benzthiazide, buthiazide, chlorothiazide, cyclopenethiazide, cyclothiazide, ethiazide, hydrochlorothiazide, methyclothiazide, penflutazide, polythiazide, teclothiazide, trichlormethiazide, triflumethazide, and the like); ambuside, amiloride, aminometradine, azosemide, bemetizide, bumetanide, butazolamide, butizide, ethacrynic acid, canrenone, chloraminophenamide, chlorazanil, chlormerodrin, chlorthalidone, clofenamide, clopamide, clorexolone, disulfamide, ethacrynic acid, ethoxzolamide, etozolon, fenquizone, furosemide, mefruside, meralluride, mercaptomerin sodium, mercumallylic acid, mersalyl, methazolamide, metolazone, muzolimine, pamabrom, paraflutizide, piretanide, protheobromine, quinethazone, scoparius, spironalactone, theobromine, ticrynafen, torsemide, triamterene, xipamide or potassium, and the like. Suitable diuretics are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

The compounds and compositions of the invention, may also be used in combination therapies with opioids and other analgesics, including, but not limited to,

narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, neurokinin 1 receptor antagonists, Substance P antagonists, neurokinin-1 receptor antagonists, sodium channel blockers, N-methyl-D-aspartate receptor antagonists, and mixtures of two or more thereof. Preferred combination therapies would be with morphine, meperidine, codeine, pentazocine, buprenorphine, butorphanol, dezocine, meptazinol, hydrocodone, oxycodone, methadone, Tramadol ((+) enantiomer), DuP 747, Dynorphine A, Enadoline, RP-60180, HN-11608, E-2078, ICI-204448, acetominophen (paracetamol), propoxyphene, nalbuphine, E-4018, filenadol, mirtentanil, amitriptyline, DuP631, Tramadol ((-) enantiomer), GP-531, acadesine, AKI-1, AKI-2, GP-1683, GP-3269, 4030W92, tramadol racemate, Dynorphine A, E-2078, AXC3742, SNX-111, ADL2-1294, ICI-204448, CT-3, CP-99,994, CP-99,994, and mixtures of two or more thereof.

The compounds and compositions of the invention can also be used in combination with inducible nitric oxide synthase (iNOS) inhibitors. Suitable iNOS inhibitors are disclosed in U. S. Patent Nos. 5,132,453 and 5,273,875, and in WO 97/38977 and WO 99/18960, the disclosures of each of which are incorporated by reference herein in their entirety.

Another embodiment of the invention provides methods to treat or prevent disorders resulting from elevated levels of COX-3 by administering to a patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one COX inhibitor, that is optionally nitrosated and/or nitrosylated. In another embodiment, the patient can be administered a therapeutically effective amount of at least one COX inhibitor, that is optionally nitrosated and/or nitrosylated, and at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a substrate for nitric oxide synthase. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one COX inhibitor, that is optionally nitrosated and/or nitrosylated, and at least one therapeutic agent, including but not limited to, steroids, nonsteroidal antiinflammatory compounds (NSAID), 5-lipoxygenase (5-LO) inhibitors, leukotriene B_4 (LTB_4) receptor antagonists, leukotriene A_4 (LTA_4) hydrolase inhibitors, 5-HT agonists, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, H_2 antagonists, antineoplastic

agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors, and, optionally, at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a substrate for nitric oxide synthase. In another embodiment, the patient can be administered a therapeutically effective amount of at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a substrate for nitric oxide synthase. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a substrate for nitric oxide synthase, and at least one therapeutic agent, including but not limited to, steroids, nonsteroidal antiinflammatory compounds (NSAID), 5-lipoxygenase (5-LO) inhibitors, leukotriene B_4 (LTB_4) receptor antagonists, leukotriene A_4 (LTA_4) hydrolase inhibitors, 5-HT agonists, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, H_2 antagonists, antineoplastic agents, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, decongestants, diuretics, sedating or non-sedating anti-histamines, inducible nitric oxide synthase inhibitors, opioids, analgesics, *Helicobacter pylori* inhibitors, proton pump inhibitors, isoprostane inhibitors. The compounds can be administered separately or in the form of a composition.

Disorders resulting from elevated levels of COX-3 (e.g., COX-3 mediated disorders) include, but are not limited to, for example, angiogenisis, arthritis, asthma, bronchitis, menstrual cramps, premature labor, tendinitis, bursitis; skin-related conditions, such as, for example, psoriasis, eczema, surface wounds, burns and dermatitis; post-operative inflammation including from ophthalmic surgery, such as, for example, cataract surgery and refractive surgery, and the like; treatment of neoplasia, such as, for example, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma), such as, for example, basal cell carcinoma, adenocarcinoma, gastrointestinal cancer, such as, for example, lip cancer, mouth cancer, esophageal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamus cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells

throughout the body, benign and cancerous tumors, growths, polyps, adenomatous polyps, including, but not limited to, familial adenomatous polyposis, fibrosis resulting from radiation therapy, and the like; treatment of inflammatory processes in diseases, such as, for example, vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like; treatment of ophthalmic diseases and disorders, such as, for example, retinitis, retinopathies, uveitis, ocular photophobia, acute injury to the eye tissue, glaucoma, inflammation of the eye and elevation of intraocular pressure and the like; treatment of pulmonary inflammation, such as, for example, those associated with viral infections and cystic fibrosis, and the like; treatment of central nervous system disorders, such as, for example, cortical dementia including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, and central nervous system damage resulting from stroke, ischemia and trauma, and the like; treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, atherosclerosis; treatment of inflammations and/or microbial infections including, for example, inflammations and/or infections of the eyes, ears, nose, throat, and/or skin; treatment and/or prevention of cardiovascular disorders, such as, for example, coronary artery disease, aneurysm, arteriosclerosis, atherosclerosis, including, but not limited to, cardiac transplant atherosclerosis, myocardial infarction, hypertension, ischemia, embolism, stroke, thrombosis, venous thrombosis, thromboembolism, thrombotic occlusion and reclusion, restenosis, angina, unstable angina, shock, heart failure, coronary plaque inflammation, bacterial-induced inflammation, such as, for example, *Chlamydia*-induced inflammation, viral induced inflammation, inflammation associated with surgical procedures, such as, for example, vascular grafting, coronary artery bypass surgery, revascularization procedures, such as, for example, angioplasty, stent placement, endarterectomy, vascular procedures involving arteries, veins, capillaries, and the like; treatment and/or prevention of urinary and/or urological disorders, such as, for example, incontinence and the like; treatment and/or prevention of endothelial dysfunctions, such as, for example, diseases accompanying these dysfunctions, endothelial damage from hypercholesterolemia, endothelial damage from hypoxia,

endothelial damage from mechanical and chemical noxae, especially during and after drug, and mechanical reopening of stenosed vessels, for example, following percutaneous transluminal angiography (PTA) and percuntaneous transluminal coronary angiography (PTCA), endothelial damage in postinfarction phase, endothelium-mediated reocculusion following bypass surgery, blood supply disturbances in peripheral arteries, as well as, cardiovascular diseases, and the like; methods for treating and/or preventing tissue deterioration, such as, for example, for organ transplants, and the like; disorders treated by the inhibition and/or prevention of activation, adhesion and infiltration of neutrophils at the site of inflammation; and disorders treated by the inhibition and/or prevention of platelet aggregation. The compounds and compositions of the invention can also be used as a pre-anesthetic medication in emergency operations to reduce the danger of aspiration of acidic gastric contents.

Another embodiment of the invention provides methods for treating and/or improving the gastrointestinal properties of the COX-2 selective inhibitors; and for decreasing or reversing renal and/or other toxicities (such as, for example, kidney toxicity, respiratory toxicity) by administering to a patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one nitrosated and/or nitrosylated COX-3 selective inhibitor. In another embodiment, the patient can be administered a therapeutically effective amount of at least one COX-3 selective inhibitor. In another embodiment, the patient can be administered a therapeutically effective amount of at least one COX-3 selective inhibitor, that is optionally nitrosated and/or nitrosylated, and at least one nitric oxide donor. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one COX-3 selective inhibitor, that is optionally nitrosated and/or nitrosylated, and at least one therapeutic agent, and, optionally, at least one nitric oxide donor. The compounds can be administered separately or in the form of a composition.

Another embodiment of the invention provides methods for improving the cardiovascular profile of COX-2 selective inhibitors by administering to a patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one nitrosated and/or nitrosylated COX-3 selective

inhibitor of the invention. In another embodiment, the patient can be administered a therapeutically effective amount of at least one COX-3 selective inhibitor, that is optionally nitrosated and/or nitrosylated, and at least one nitric oxide donor. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one COX-3 selective inhibitor, that is optionally nitrosated and/or nitrosylated, at least one of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors, antiplatelet agents, thrombin inhibitors, thromboxane inhibitors, and, optionally, at least one nitric oxide donor. The compounds can be administered separately or in the form of a composition.

When administered separately, the COX inhibitor, that is optionally nitrosated and/or nitrosylated, can be administered about the same time as part of the overall treatment regimen, i.e., as a combination therapy. "About the same time" includes administering the COX inhibitor, that is optionally nitrosated and/or nitrosylated, simultaneously, sequentially, at the same time, at different times on the same day, or on different days, as long as they are administered as part of an overall treatment regimen, i.e., combination therapy or a therapeutic cocktail.

When administered in vivo, the compounds and compositions of the invention can be administered in combination with pharmaceutically acceptable carriers and in dosages described herein. When the compounds and compositions of the invention are administered as a combination of at least one COX inhibitor and/or at least one nitrosated and/or nitrosylated COX inhibitor and/or at least one nitric oxide donor and/or therapeutic agent, they can also be used in combination with one or more additional compounds which are known to be effective against the specific disease state targeted for treatment. The nitric oxide donors, therapeutic agents and/or other additional compounds can be administered simultaneously with, subsequently to, or prior to administration of the COX inhibitor and/or nitrosated and/or nitrosylated COX inhibitor.

The compounds and compositions of the invention can be administered by any available and effective delivery system including, but not limited to, orally, bucally, parenterally, by inhalation spray, by topical application, by injection, transdermally, or rectally (e.g., by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles, as desired. Parenteral includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Transdermal compound administration, which is known to one skilled in the art, involves the delivery of pharmaceutical compounds via percutaneous passage of the compound into the systemic circulation of the patient. Topical administration can also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. Other components can be incorporated into the transdermal patches as well. For example, compositions and/or transdermal patches can be formulated with one or more preservatives or bacteriostatic agents including, but not limited to, methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chloride, and the like. Dosage forms for topical administration of the compounds and compositions can include creams, sprays, lotions, gels, ointments, eye drops, nose drops, ear drops, and the like. In such dosage forms, the compositions of the invention can be mixed to form white, smooth, homogeneous, opaque cream or lotion with, for example, benzyl alcohol 1% or 2% (wt/wt) as a preservative, emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water and sorbitol solution. In addition, the compositions can contain polyethylene glycol 400. They can be mixed to form ointments with, for example, benzyl alcohol 2% (wt/wt) as preservative, white petrolatum, emulsifying wax, and tenox II (butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, can be impregnated with the compositions in solution, lotion, cream, ointment or other such form can also be used for topical application. The compositions can also be applied topically using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the composition and laminated to an impermeable backing.

Solid dosage forms for oral administration can include capsules, tablets, effervescent tablets, chewable tablets, pills, powders, sachets, granules and gels. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms can also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, effervescent tablets, and pills, the dosage forms can also comprise buffering agents. Soft gelatin capsules can be prepared to contain a mixture of the active compounds or compositions of the invention and vegetable oil. Hard gelatin capsules can contain granules of the active compound in combination with a solid, pulverulent carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives of

gelatin. Tablets and pills can be prepared with enteric coatings.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Suppositories for vaginal or rectal administration of the compounds and compositions of the invention, such as for treating pediatric fever and the like, can be prepared by mixing the compounds or compositions with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at room temperature but liquid at rectal temperature, such that they will melt in the rectum and release the drug.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. Sterile fixed oils are also conventionally used as a solvent or suspending medium.

The compositions of this invention can further include conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, for example, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, surfactants, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, and the like. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds. For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. Aqueous suspensions may contain substances

which increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

The composition, if desired, can also contain minor amounts of wetting agents, emulsifying agents and/or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like.

Various delivery systems are known and can be used to administer the compounds or compositions of the invention, including, for example, encapsulation in liposomes, microbubbles, emulsions, microparticles, microcapsules and the like. The required dosage can be administered as a single unit or in a sustained release form.

The bioavailability of the compositions can be enhanced by micronization of the formulations using conventional techniques such as grinding, milling, spray drying and the like in the presence of suitable excipients or agents such as phospholipids or surfactants.

Sustained release dosage forms of the invention may comprise microparticles and/or nanoparticles having a therapeutic agent dispersed therein or may comprise the therapeutic agent in pure, preferably crystalline, solid form. For sustained release administration, microparticle dosage forms comprising pure, preferably crystalline, therapeutic agents are preferred. The therapeutic dosage forms of this aspect of the invention may be of any configuration suitable for sustained release.

Nanoparticle sustained release therapeutic dosage forms are preferably biodegradable and, optionally, bind to the vascular smooth muscle cells and enter those cells, primarily by endocytosis. The biodegradation of the nanoparticles occurs over time (e.g., 30 to 120 days; or 10 to 21 days) in prelysosomic vesicles and lysosomes. Preferred larger microparticle therapeutic dosage forms of the invention release the therapeutic agents for subsequent target cell uptake with only a few of the smaller microparticles entering the cell by phagocytosis. A practitioner in the art will appreciate that the precise mechanism by which a target cell assimilates and metabolizes a dosage form of the invention depends on the

morphology, physiology and metabolic processes of those cells. The size of the particle sustained release therapeutic dosage forms is also important with respect to the mode of cellular assimilation. For example, the smaller nanoparticles can flow with the interstitial fluid between cells and penetrate the infused tissue. The larger microparticles tend to be more easily trapped interstitially in the infused primary tissue, and thus are useful to deliver anti-proliferative therapeutic agents.

Particular sustained release dosage forms of the invention comprise biodegradable microparticles or nanoparticles. More particularly, biodegradable microparticles or nanoparticles are formed of a polymer containing matrix that biodegrades by random, nonenzymatic, hydrolytic scissioning to release therapeutic agent, thereby forming pores within the particulate structure.

In a particular embodiment, the compositions of the invention are orally administered as a sustained release tablet or a sustained release capsule. For example, the sustained release formulations can comprise a therapeutically effective amount of at least one COX inhibitors, that is optionally nitrosated and/or nitrosylated, or the sustained release formulations can comprise a therapeutically effective amount of at least one COX inhibitor, that is optionally nitrosated and/or nitrosylated, and NO donor, or the sustained release formulations can comprise a therapeutically effective amount of at least one COX inhibitor, that is optionally nitrosated and/or nitrosylated, and therapeutic agents, or the sustained release formulations can comprise a therapeutically effective amount of at least one COX inhibitor, that is optionally nitrosated and/or nitrosylated, NO donors, and therapeutic agents.

The preferred methods of administration of the COX inhibitors and compositions for the treatment of gastrointestinal disorders are orally, bucally or by inhalation. The preferred methods of administration for the treatment of inflammation and microbial infections are orally, bucally, topically, transdermally or by inhalation.

The compounds and compositions of the invention can be formulated as pharmaceutically acceptable salt forms. Pharmaceutically acceptable salts include, for example, alkali metal salts and addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid and the like. Appropriate organic acids include, but

are not limited to, aliphatic, cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids, such as, for example, formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesuifonic, sulfanilic, stearic, algenic, β-hydroxybutyric, cyclohexylaminosulfonic, galactaric and galacturonic acid and the like. Suitable pharmaceutically-acceptable base addition salts include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine and the like. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

While individual needs may vary, determination of optimal ranges for effective amounts of the compounds and/or compositions is within the skill of the art. Generally, the dosage required to provide an effective amount of the compounds and compositions, which can be adjusted by one of ordinary skill in the art, will vary depending on the age, health, physical condition, sex, diet, weight, extent of the dysfunction of the recipient, frequency of treatment and the nature and scope of the dysfunction or disease, medical condition of the patient, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound used, whether a drug delivery system is used, and whether the compound is administered as part of a drug combination.

The amount of a given COX inhibitor of the invention that will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques, including reference to Goodman and Gilman, supra; The Physician's Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 1995; and Drug Facts and Comparisons, Inc., St. Louis, MO, 1993. The precise dose to be used in the formulation will also depend on the route of administration, and the seriousness of the

disease or disorder, and should be decided by the physician and the patient's circumstances.

The amount of nitric oxide donor in a pharmaceutical composition can be in amounts of about 0.1 to about 10 times the molar equivalent of the COX inhibitor. The usual daily doses of the COX inhibitors are about 0.001 mg to about 140 mg/kg of body weight per day, preferably 0.005 mg to 30 mg/kg per day, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammations may be effectively treated by the administration of from about 0.01 mg to 50 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day. The compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, and most preferably once per day. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems and are in the same ranges or less than as described for the commercially available compounds in the Physician's Desk Reference, supra.

The disclosure of each patent, patent application and publication cited or described in the present specification is hereby incorporated by reference herein in its entirety.

Although the invention has been set forth in detail, one skilled in the art will appreciate that numerous changes and modifications can be made to the invention, and that such changes and modifications can be made without departing from the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A method for treating a disorder resulting from elevated levels of cyclooxygenase-3 comprising administering to a patient in need thereof a therapeutically effective amount of at least one cyclooxygenase inhibitor or a pharmaceutically acceptable salt thereof.

2 The method of claim 1, further comprising administering a pharmaceutically acceptable carrier.

3. The method of claim 1, wherein the cyclooxyenase inhibitor is a non-steroidal antiinflammatory compound, a cyclooxygenase-1 selective inhibitor, a cyclooxygenase-2 selective inhibitor, a cyclooxygenase-3 selective inhibitor, a cyclooxygenase-1 and cyclooxygenase-2 selective inhibitor, a cyclooxygenase-1 and cyclooxygenase-3 selective inhibitor, a cyclooxygenase-2 and cyclooxygenase-3 selective inhibitor, a cyclooxygenase-1, cyclooxygenase-2 and cyclooxygenase-3 selective inhibitor or a mixture of two or more thereof.

4. The method of claim 1, wherein the cyclooxygenase inhibitor has at least one NO group, at least one NO_2 group or at least one NO and NO_2 group, wherein the at least one NO group, the least one NO_2 group or the at least one NO and NO_2 group is linked to the cyclooxygenase inhibitor through an oxygen atom, a nitrogen atom or a sulfur atom.

5. The method of claim 1, wherein the disorder resulting from elevated levels of cyclooxygenase-3 is angiogenesis, arthritis, asthma, bronchitis, a menstrual cramp, premature labor, tendinitis, bursitis, a skin-related condition, neoplasia, an inflammatory process in a disease, an ophthalmic disorder, a pulmonary inflammation, a central nervous system disorder, allergic rhinitis, a respiratory distress syndrome, an endotoxin shock syndrome, atherosclerosis, a microbial infection, a cardiovascular disorder, a urinary disorder, a urological disorder, an endothelial dysfunction, organ deterioration, tissue deterioration, or activation, adhesion and infiltration of neutrophils at the site of inflammation.

6. The method of claim 5, wherein the neoplasia is a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung

cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy.

7. The method of claim 5, wherein the central nervous system disorder is cortical dementia, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, or central nervous system damage resulting from stroke, ischemia or trauma.

8. The method of claim 1, further comprising administering (i) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase; (ii) at least one therapeutic agent; or (iii) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and at least one therapeutic agent.

9. The method of claim 8, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase (5-LO) inhibitor, a leukotriene B_4 receptor antagonist, a leukotriene A_4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H_2 antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a *Helicobacter pylori* inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

10. The method of claim 8, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

11. The method of claim 10, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione, or S-nitroso-cysteinyl-glycine.

12. The method of claim 10, wherein the S-nitrosothiol is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) H_2N-CH(CO_2H)-(CH_2)$_m$-C(O)NH-CH(CH_2SNO)-C(O)NH-CH_2-CO_2H;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring. a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, an arylsulfonyloxy, a urea, a nitro, -T-Q'-, or –($C(R_g)(R_h)$)$_k$-T-Q' or R_e and R_f taken together are an oxo, a methanthial, a heterocyclic ring, a cycloalkyl group, an oxime, a hydrazone or a bridged cycloalkyl group; Q' is -NO or -NO_2; and T is independently a covalent bond, a carbonyl, an oxygen, -$S(O)_o$- or -$N(R_a)R_i$-, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyloxy, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, -CH_2-C(T-Q')(R_g)(R_h), or -(N_2O_2-)$^-$•M^+, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is -CH_2-C(T-Q')(R_g)(R_h) or -(N_2O_2-)•M^+; then "-T-Q'" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group; and R_g and R_h at each occurrence are independently R_e.

13. The method of claim 8, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated L-homoarginine, nitrosylated L-homoarginine), citrulline, ornithine,

glutamine, lysine, an arginase inhibitor or a nitric oxide mediator.

14. The method of claim 8, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O- or ON-N- group;

(ii) a compound that comprises at least one O_2N-O-, O_2N-N- or O_2N-S- or group;

(iii) a N-oxo-N-nitrosoamine having the formula: $R^{1"}R^{2"}$N-N(O-M^+)-NO, wherein $R^{1"}$ and $R^{2"}$ are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

15. The method of claim 14, wherein the compound comprising at least one ON-O- or ON-N- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, an ON-O-heterocyclic compound or an ON-N-heterocyclic compound.

16. The method of claim 14, wherein compound comprising at least one O_2N-O-, O_2N-N- or O_2N-S- group is an O_2N-O-polypeptide, an O_2N-N-polypeptide, an O_2N-S-polypeptide, an O_2N-O-amino acid, O_2N-N-amino acid, O_2N-S-amino acid, an O_2N-O-sugar, an O_2N-N-sugar, O_2N-S-sugar, an O_2N-O-oligonucleotide, an O_2N-N-oligonucleotide, an O_2N-S-oligonucleotide, , a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-S-hydrocarbon, an O_2N-O-heterocyclic compound, an O_2N-N-heterocyclic compound or an O_2N-S-heterocyclic compound.

17. A method for improving a gastrointestinal property of a

cyclooxygenase-2 inhibitor, for treating or reversing renal and/or respiratory toxicity of a cyclooxygenase-2 inhibitor or for improving a cardiovascular profile of a cyclooxygenase-2 inhibitor in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one cyclooxygenase-3 selective inhibitor or a pharmaceutically acceptable salt thereof.

18. The method of claim 17, further comprising administering a pharmaceutically acceptable carrier.

19. The method of claim 17, wherein the cyclooxygenase-3 selective inhibitor has at least one NO group, at least one NO_2 group or at least one NO and NO_2 group, wherein the at least one NO group, the least one NO_2 group or the at least one NO and NO_2 group is linked to the cyclooxygenase-3 selective inhibitor through an oxygen atom, a nitrogen atom or a sulfur atom.

20. The method of claim 17, further comprising administering (i) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase; (ii) at least one therapeutic agent; or (iii) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and at least one therapeutic agent.

21. A method for treating a disorder resulting from elevated levels of cyclooxygenase-3 comprising administering to a patient in need thereof a therapeutically effective amount of (i) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase; or (ii) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and at least one therapeutic agent.

22. The method of claim 21, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

23. The method of claim 22, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione, or S-nitroso-cysteinyl-

glycine.

24. The method of claim 22, wherein the S-nitrosothiol is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring. a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, an arylsulfonyloxy, a urea, a nitro, -T-Q'-, or $-(C(R_g)(R_h))_k\text{-}T\text{-}Q'$ or R_e and R_f taken together are an oxo, a methanthial, a heterocyclic ring, a cycloalkyl group, an oxime, a hydrazone or a bridged cycloalkyl group; Q' is -NO or $-NO_2$; and T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyloxy, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, $-CH_2\text{-}C(T\text{-}Q')(R_g)(R_h)$, or $-(N_2O_2\text{-})^-\bullet M^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-CH_2\text{-}C(T\text{-}Q')(R_g)(R_h)$ or $-(N_2O_2\text{-})\bullet M^+$; then "-T-Q'" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group; and R_g and R_h at each occurrence are independently R_e.

25. The method of claim 21, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is L-

arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated L-homoarginine, nitrosylated L-homoarginine), citrulline, ornithine, glutamine, lysine, an arginase inhibitor or a nitric oxide mediator.

26. The method of claim 21, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O- or ON-N- group;

(ii) a compound that comprises at least one O_2N-O-, O_2N-N- or O_2N-S- or group;

(iii) a N-oxo-N-nitrosoamine having the formula: $R^{1"}R^{2"}$N-N(O-M^+)-NO, wherein $R^{1"}$ and $R^{2"}$ are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

27. The method of claim 26, wherein the compound comprising at least one ON-O- or ON-N- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, an ON-O-heterocyclic compound or an ON-N-heterocyclic compound.

28. The method of claim 26, wherein compound comprising at least one O_2N-O-, O_2N-N- or O_2N-S- group is an O_2N-O-polypeptide, an O_2N-N-polypeptide, an O_2N-S-polypeptide, an O_2N-O-amino acid, O_2N-N-amino acid, O_2N-S-amino acid, an O_2N-O-sugar, an O_2N-N-sugar, O_2N-S-sugar, an O_2N-O-oligonucleotide, an O_2N-N-oligonucleotide, an O_2N-S-oligonucleotide, , a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-S-hydrocarbon, an O_2N-O-

heterocyclic compound, an O_2N-N-heterocyclic compound or an O_2N-S-heterocyclic compound.

29. The method of claim 21, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a 5-lipoxygenase (5-LO) inhibitor, a leukotriene B_4 receptor antagonist, a leukotriene A_4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H_2 antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a *Helicobacter pylori* inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

30. The method of claim 21, wherein the disorder resulting from elevated levels of cyclooxygenase-3 is angiogenesis, arthritis, asthma, bronchitis, a menstrual cramp, premature labor, tendinitis, bursitis, a skin-related condition, neoplasia, an inflammatory process in a disease, an ophthalmic disorder, a pulmonary inflammation, a central nervous system disorder, allergic rhinitis, a respiratory distress syndrome, an endotoxin shock syndrome, atherosclerosis, a microbial infection, a cardiovascular disorder, a urinary disorder, a urological disorder, an endothelial dysfunction, organ deterioration, tissue deterioration, or activation, adhesion and infiltration of neutrophils at the site of inflammation.

31. The method of claim 30, wherein the neoplasia is a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy.

32. The method of claim 30, wherein the central nervous system disorder is cortical dementia, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, or central nervous system damage resulting from stroke, ischemia or trauma.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TREATMENT OF CYCLOOXYGENASE-3 MEDIATED DISEASES AND DISORDERS

(57) Abstract: The invention describes methods for treating and/or preventing diseases and/or disorders resulting from elevated levels of cyclooxygenase-3 comprising administration of at least one cyclooxygenase inhibitor that is optionally nitrosated and/or nitrosylated, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase and/or at least one therapeutic agent. The invention also provides methods for treating and/or preventing diseases and/or disorders resulting from elevated levels of cyclooxygenase-3 comprising administration of at least compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and, optionally, at least one therapeutic agent. The invention also provides methods for treating and/or improving the gastrointestinal properties of cyclooxygenase-2 (COX-2) selective inhibitors; for treating and/or preventing renal and other toxicities of COX-2 selective inhibitors; for treating and for improving the cardiovascular profile of COX-2 selective inhibitors comprising administration of at least one cyclooxygenase-3 (COX-3) inhibitor that is optionally nitrosated and/or nitrosylated, and, optionally, at least nitric oxide donor and/or at least one therapeutic agent. The cyclooxygenase inhibitors of the invention include, but are not limited to, cyclooxygenase-3 selective inhibitors, cyclooxygenase-2 selective inhibitors, cyclooxygenase-1 selective inhibitors, non-steroidal anti-inflammatory compounds, and mixtures of two or more thereof.

WO 2004/024186 A3

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61K31/00 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COLIN DOLLERY: "THERAPEUTIC DRUGS, SECOND EDITION" THERAPEUTIC DRUGS, XX, XX, 1999, pages a216-a221, XP002266593	1-16
Y	Aspirin the whole document	8-16

X	COLIN DOLLERY: "THERAPEUTIC DRUGS, SECOND EDITION" THERAPEUTIC DRUGS, XX, XX, 1999, pages I1-I3, XP002266594	1-16
Y	Ibuprofen the whole document	8-16

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2004	18. 06. 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herrera, S

1

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SCHWAB J M ET AL: "COX-3: just another COX or the solitary elusive target of paracetamol?" LANCET THE, LANCET LIMITED. LONDON, GB, vol. 361, no. 9362, 22 March 2003 (2003-03-22), pages 981-982, XP004415846 ISSN: 0140-6736	1-16
T	the whole document	
Y	WO 96/16645 A (RADOMSKI MAREK ;BELDER ADAM JULIAN DE (GB); KING S COLLEGE LONDON) 6 June 1996 (1996-06-06) page 1, lines 1-8; claims	8-16

1

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-16

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Claims Nos.: -

Present claims 1-16 relate to methods involing an extremely large number of possible compounds and combinations. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds and combinations claimed. It is especially pointed out that the application does not contain any specific examples. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for the general idea of the invention, i.e. the general use of COX inhibitors in the treatment od the diseases said to be resulting from elevated levels of COX-3.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-16

   Use of COX inhibitors for the treatment of diseases resulting from elevated levels of COX-3.

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2. claims: 17-20

   Use of a COX-3 inhibitor for improving the negative effects of a COX-2 inhibitor

   ---

3. claims: 21-32

   Use of a compound which releases of increases the level of nitric oxide in the of diseases resulting from elevated levels of COX-3.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9616645 A	06-06-1996	AU 3878895 A	19-06-1996
		WO 9616645 A1	06-06-1996